



S/N 09/840627

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Pavel A. Krasutsky  
Serial No.: 09/840627  
Filed: April 23, 2001  
Title: METHOD FOR MANUFACTURING BETULINIC ACID

Examiner: Deborah Carr  
Group Art Unit: #8  
Docket: 1339.018US3

PETITION TO WITHDRAW HOLDING OF ABANDONMENT

Box DAC  
Commissioner for Patents  
Washington, D.C. 20231

A Notice of Abandonment mailed January 28, 2003 for the above-identified patent application was received by our office February 3, 2003. The Notice alleges that Applicant failed to respond to the Office Action mailed on June 19, 2002. The Office Action set a three-month period of response, which expired on September 19, 2002.

However, Applicant filed a responsive Amendment on August 2, 2002, with a Certificate of Mailing reflecting the same. In return, Applicant received a PTO-stamped postcard acknowledging receipt of the Amendment by the USPTO August 9, 2002. A copy of the timely filed Amendment and the PTO-stamped postcard are attached as Exhibits A and B, respectively.

Thus, there is no action or omission by Applicant to support a holding that the above-identified application was or is abandoned. Accordingly, the abandonment holding should be withdrawn and prosecution resumed as soon as possible.

It is Applicant's understanding that no fee is required for a petition to withdraw a holding of abandonment. (See MPEP 711.03(c)), and therefore no fee is enclosed. However, if a fee is required, please charge it to Deposit Account No. 19-0743.

Respectfully submitted,

PAVEL A. KRASUTSKY

By his Representatives,

SCHWEGMAN, LUNDBERG, WOESSNER & KLUTH, P.A.  
P.O. Box 2938  
Minneapolis, MN 55402  
612-359-3261

Date 3/10/03

By [Signature]  
Gary J Speier  
Reg. No. 45,458

CERTIFICATE UNDER 37 CFR 1.8: The undersigned hereby certifies that this correspondence is being deposited with the United States Postal Service with sufficient postage as first class mail, in an envelope addressed to: Commissioner for Patents, Washington, D.C. 20231 on this 11 day of March, 2003.

Gina M Unhus

Gina Unhus

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In re Patent Application of: Pavel A. Krasutsky

Title: METHOD FOR MANUFACTURING BETULINIC ACID

Serial No.: 09/840,627

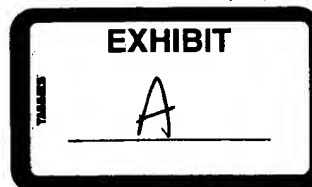
Filing Date: April 23, 2001

Receipt is hereby acknowledged for the following in the United States Patent and Trademark Office:

**CONTENTS:** An Amendment and Response (12 Pages); Clean Version of the Pending Claims (10 pgs.); Clean Version of Abstract (1 pg.); a Return Postcard and TRANSMITTAL SHEET.

Mailed: August 2, 2002  
GJS/dmp

Docket No.: 600.460US3  
Due Date: September 19, 2002





In re Patent Application of: Pavel A. Krasutsky  
Title: METHOD FOR MANUFACTURING BETULINIC ACID  
Serial No.: 09/840,627 Filing Date: April 23, 2001.

Receipt is hereby acknowledged for the following in the United States Patent and Trademark Office:

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Mailed: August 2, 2002  
GJS/dmp



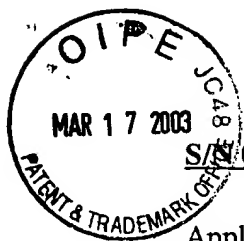
Docket No.: 600.460US3  
Due Date: September 19, 2002

01339.018US3



EXHIBIT

B



S/N 09/840,627

**PATENT**

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

Applicant: Pavel A. Krasutsky

Examiner: Deborah D. Carr

Serial No.: 09/840,627

Group Art Unit: 1621

Filed: April 23, 2001

Docket: 600.460US3

Title: METHOD FOR MANUFACTURING BETULINIC ACID

**AMENDMENT AND RESPONSE UNDER 37 CFR § 1.111**

Commissioner for Patents  
Washington, D.C. 20231

Applicant has reviewed the Office Action mailed on June 19, 2002. Please amend the above-identified patent application as follows.

**IN THE ABSTRACT**

Please make the paragraph substitutions indicated in the appendix entitled Clean Version of Amended Abstract. The specific changes incorporated in the substitute Abstract are shown in the following marked-up version of the Abstract:

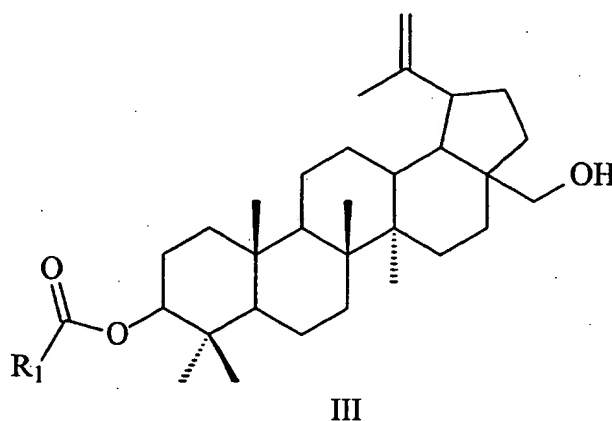
**ABSTRACT**

The present invention provides a method for preparing an ester of betulin[-] at the 3-  
[acetate]position, e.g., betulin-3-acetate, including [alcoholyzing]the selective alcoholysis of a  
betulin-3,28-[dibenzoate;]diester, e.g., betulin-3,28-diacetate; a [process]method for preparing  
betulin-3-acetate including[:] (1) acetylating betulin to provide betulin-3,28-  
[dibenzoate]diacetate and (2) the alcoholysis of[alcoholyzing] betulin-3,28-[dibenzoate]diacetate  
to provide betulin-3-acetate; and a method [process] for preparing betulinic acid[:] (1) acetylating  
betulin to provide betulin-3,28-[dibenzoate;]diacetate, (2) the alcoholysis of  
[alcoholyzing]betulin-3,28-[dibenzoate]diacetate to provide betulin-3-acetate[:], (3) oxidizing  
betulin-3-acetate to provide betulinic aldehyde-3-acetate[:], (4) oxidizing betulinic aldehyde-3-  
acetate to provide betulinic acid-3-acetate[:], and (5) deprotecting betulinic acid-3-acetate to  
provide betulinic acid.

### IN THE CLAIMS

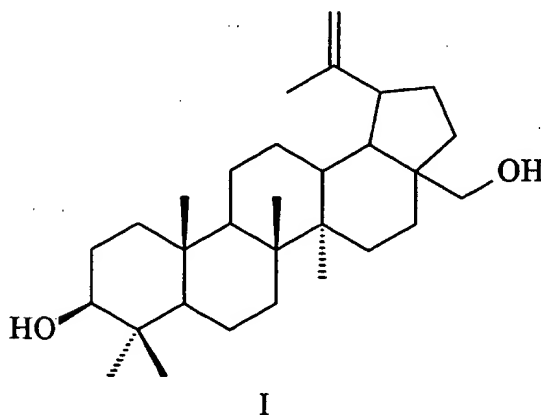
Please substitute the claim set in the appendix entitled Clean Version of Pending Claims for the previously pending claim set. The substitute claim set is intended to reflect amendment of previously pending claims 1, 5, 6, 7, 8, 12, 13, and 22. The specific amendments to individual claims are detailed in the following marked up set of claims.

1. (ONCE AMENDED) A process for preparing a compound of formula III

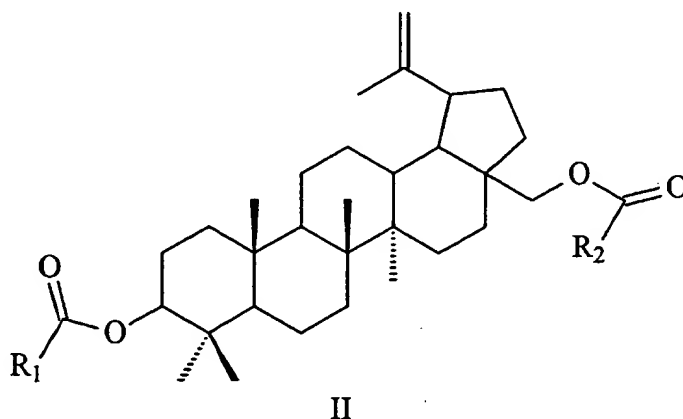


comprising:

- (1) acylating a compound of formula I



to provide a corresponding compound of formula II



wherein R<sub>1</sub> and R<sub>2</sub> are each independently [any suitable organic group] (C<sub>1</sub>-C<sub>10</sub>)alkyl, (C<sub>2</sub>-C<sub>10</sub>)alkenyl, (C<sub>2</sub>-C<sub>10</sub>)alkynyl, or (C<sub>6</sub>-C<sub>10</sub>)aryl, wherein any alkyl, alkenyl, alkynyl, or aryl of R<sub>1</sub> and R<sub>2</sub> can be optionally substituted with one or more halo, nitro, cyano, trifluoromethyl, hydroxy, SR or NRR, wherein each R is independently H or (C<sub>1</sub>-C<sub>10</sub>)alkyl; and

(2) alcoholyzing a compound of formula II to provide a corresponding compound of formula III.

2. The process of claim 1 wherein the acylating comprises heating to reflux in acetic acid and acetic anhydride for about 2 hours to about 5 hours.

3. The process of claim 1 wherein the acylating comprises heating in pyridine and benzoyl chloride at about 50°C to about 60°C for about 20 hours to about 30 hours.

4. The process of claim 1 wherein the alcoholyzing comprises heating in the presence of an aluminum alkoxide and an anhydrous alcohol.

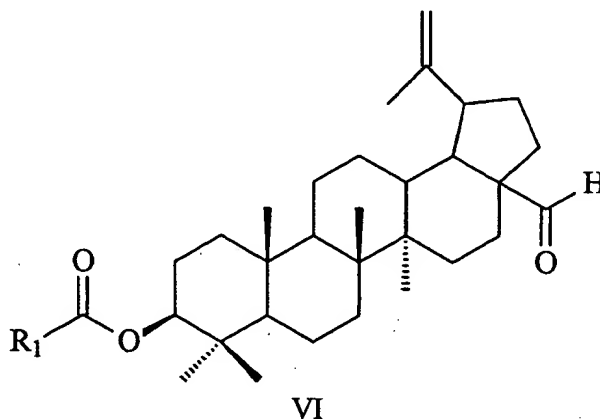
5. (ONCE AMENDED) The process of claim [1 wherein R<sub>1</sub> and R<sub>2</sub> are each (C<sub>1</sub>-C<sub>10</sub>)alkyl]  
4 wherein the aluminum alkoxide is aluminum isopropoxide.

6. (ONCE AMENDED) The process of claim [5 wherein (C<sub>1</sub>-C<sub>10</sub>)alkyl is methyl] 4 wherein the alcohol is isopropanol.

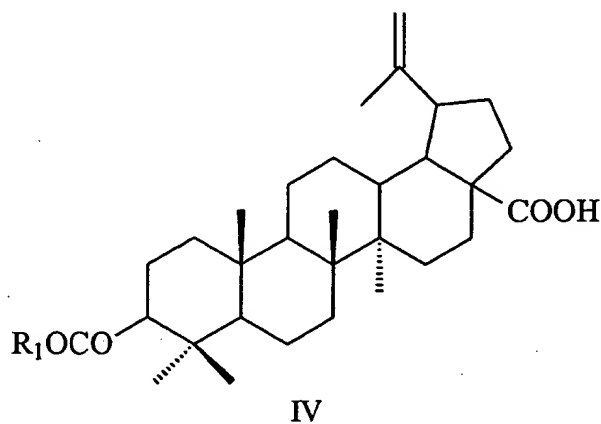
7. (ONCE AMENDED) The process of claim [6 wherein the aluminum alkoxide is aluminum isopropoxide] 1 wherein the acylating is carried out employing an acid anhydride, a carboxylic acid, or an acid chloride.

8. (ONCE AMENDED) The process of claim [1 wherein the alcohol is isopropanol] 1 wherein the acylating is carried out employing acetic anhydride, benzoyl anhydride, maleic anhydride, phthalic anhydride, succinic anhydride, acetic acid, benzoic acid, acetyl chloride, pentanoyl chloride, or benzoyl chloride.

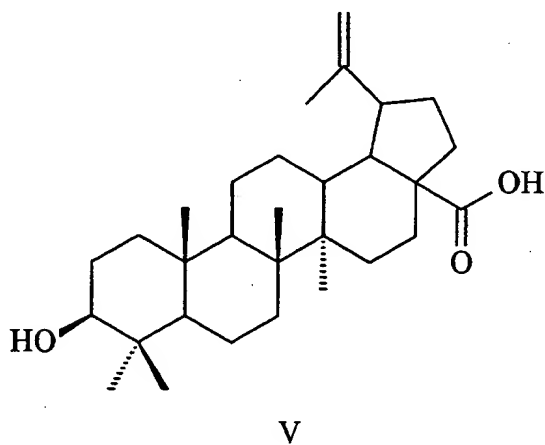
9. The process of claim 1 further comprising oxidizing the compound of formula III to provide a compound of formula VI



10. The process of claim 9 further comprising oxidizing the compound of formula VI to provide a compound of formula IV

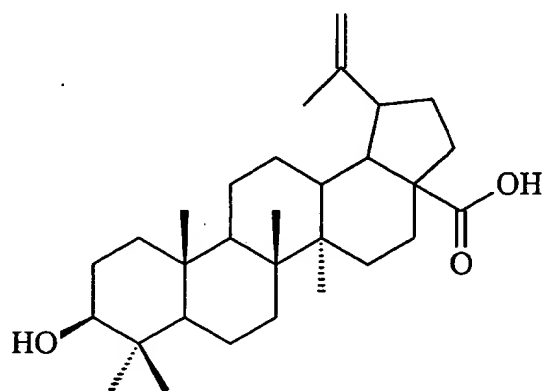


11. The process of claim 10 further comprising deprotecting the compound of formula IV to provide a compound of formula V



12. (ONCE AMENDED) A process for preparing the compound of formula V

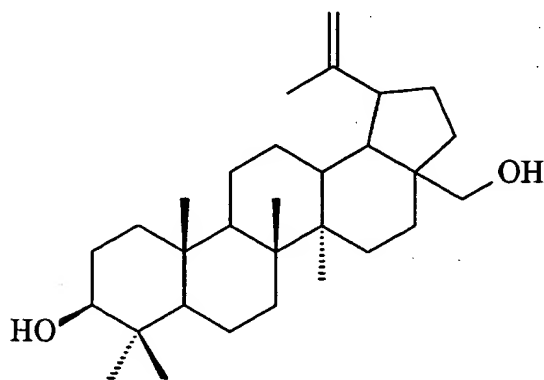




V

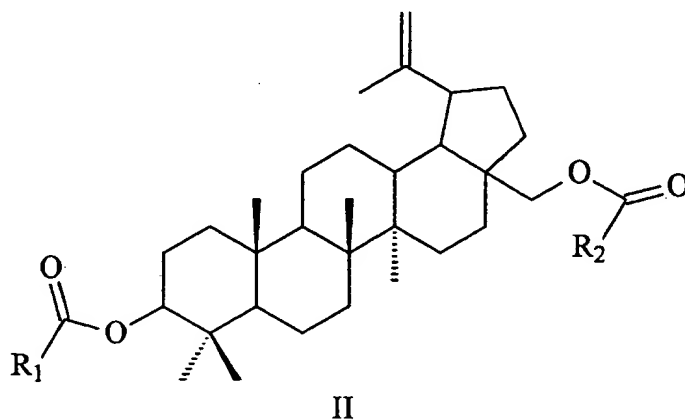
comprising:

(1) acylating a compound of formula I



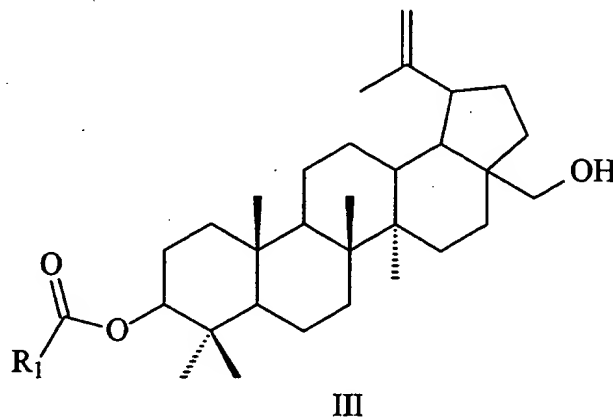
I

to provide a corresponding compound of formula II

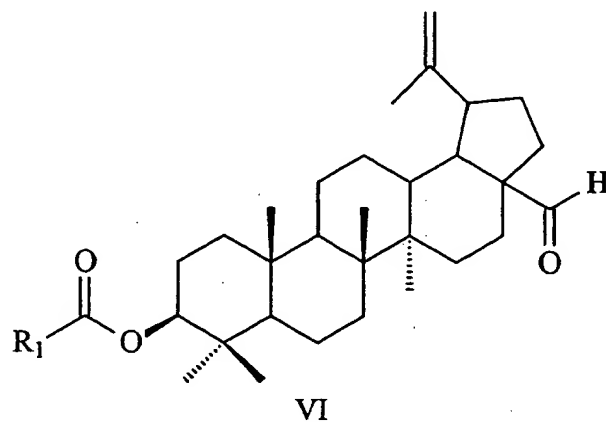


wherein  $R_1$  and  $R_2$  are each independently [any suitable organic group]  $(C_1-C_{10})$ alkyl,  $(C_2-C_{10})$ alkenyl,  $(C_2-C_{10})$ alkynyl, or  $(C_6-C_{10})$ aryl, wherein any alkyl, alkenyl, alkynyl, or aryl of  $R_1$  and  $R_2$  can be optionally substituted with one or more halo, nitro, cyano, trifluoromethyl, hydroxy, SR or NRR, wherein each R is independently H or  $(C_1-C_{10})$ alkyl;

(2) alcoholyzing a compound of formula II to provide a corresponding compound of formula III;

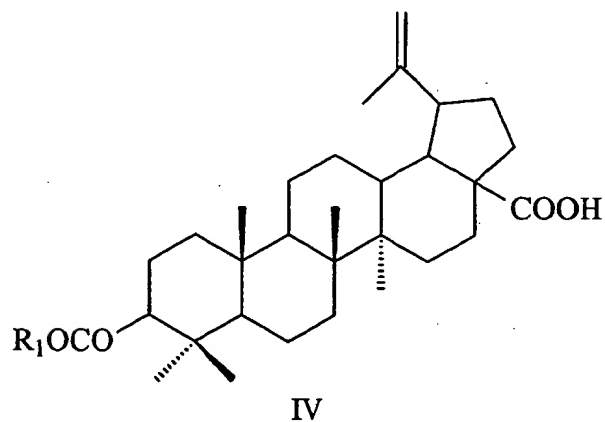


(3) oxidizing the compound of formula III to provide a corresponding compound of formula VI;



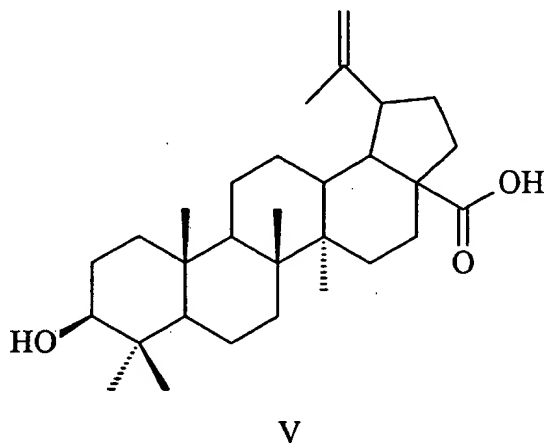
(4) oxidizing the compound of formula VI to provide a compound of formula IV;

and



(5) deprotecting the compound of formula IV to provide the compound of formula

V.



13. (ONCE AMENDED) The process of claim 12 wherein [R<sub>1</sub> and R<sub>2</sub> are each methyl] the alcoholizing is carried out for about 0.5 hours to about 5 hours.

14. The process of claim 12 wherein the alcoholizing comprises heating the compound of formula II in the presence of an aluminum alkoxide and an anhydrous alcohol.

15. The process of claim 14 wherein the aluminum alkoxide is aluminum isopropoxide.

16. The process of claim 14 wherein the alcohol is isopropanol.

17. The process of claim 12 wherein the acylating comprises heating to reflux in acetic acid and acetic anhydride for about 2 hours to about 5 hours.

18. The process of claim 12 wherein the acylating comprises heating in pyridine and benzoyl chloride at about 50°C to about 60°C for about 20 hours to about 30 hours.

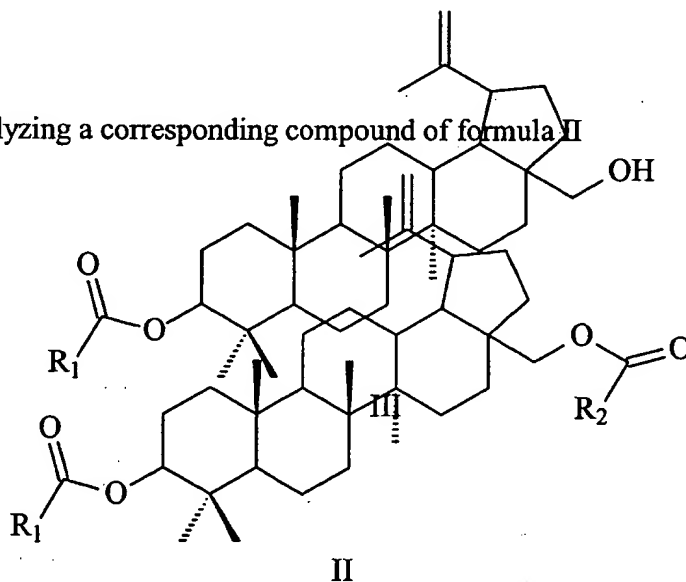
19. The process of claim 12 wherein the oxidizing of compound III to compound VI comprises palladium acetate, molecular sieves, and oxygen in trifluoromethylbenzene and pyridine at about 80°C to about 85°C for about 0.5 hour to about 4 hours.

20. The process of claim 12 wherein the oxidizing of compound VI to compound IV comprises oxygen and Cobalt (III) acetylacetonate in trifluoromethylbenzene at 60-65°C for about 0.5 hour to about 2 hours.

21. The process of claim 12 wherein the deprotecting comprises heating to reflux in methanol, water and sodium hydroxide.

22. (ONCE AMENDED) A process for preparing a compound of formula III

comprising: alcoholyzing a corresponding compound of formula II



wherein R<sub>1</sub> and R<sub>2</sub> are each independently [any suitable organic group] (C<sub>1</sub>-C<sub>10</sub>)alkyl, (C<sub>2</sub>-C<sub>10</sub>)alkenyl, (C<sub>2</sub>-C<sub>10</sub>)alkynyl, or (C<sub>6</sub>-C<sub>10</sub>)aryl, wherein any alkyl, alkenyl, alkynyl, or aryl of R<sub>1</sub> and R<sub>2</sub> can be optionally substituted with one or more halo, nitro, cyano, trifluoromethyl, hydroxy, SR or NRR, wherein each R is independently H or (C<sub>1</sub>-C<sub>10</sub>)alkyl; to provide the compound of formula III.

### REMARKS

Applicant has carefully reviewed and considered the Office Action mailed on June 19, 2002, and the references cited therewith.

Claims 1, 5, 6, 7, 8, 12, 13, and 22 have been amended, no claims have been canceled, and no claims have been added; as a result, claims 1-22 are now pending in this application. Support for the amendments to the claims can be found in the specification as originally filed. Specifically, support for the amendment to claims 1, 12, and 22 can be found, e.g., at page 8, line 24 to page 9, line 2. Support for the amendment to claim 5 can be found, e.g., at claim 7 as originally filed. Support for the amendment to claim 6 can be found, e.g., at claim 8 as originally filed. Support for the amendment to claim 7 can be found, e.g., page 9, lines 3-10. Support for the amendment to claim 8 can be found, e.g., page 9, lines 3-10. Support for the amendment to claim 13 can be found, e.g., page 11, lines 22-23. As such, no new matter has been added by way of this amendment.

### Double Patenting Rejection

Claims 1-3, 5-6, 8-13 and 17-22 were rejected under the statutory double patenting (35 U.S.C. 101) over claims 4, 7 and 14-16 of U.S. Patent No. 6,232,481. Applicant respectfully traverses this rejection.

Claims 1, 5, 6, 7, 8, 12, 13, and 22 have been amended. Applicant believes the amendments to the claims obviate the double patenting rejection.

Withdrawal of the double patenting rejection is respectfully requested.

### Allowable Subject Matter

Claims 4, 7 and 14-16 were objected to as being dependent upon a rejected base claim, but were indicated to be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims. It is respectfully pointed out that Applicant believes the amendments to the claims obviate this objection.

Conclusion

Applicant respectfully submits that the claims are in condition for allowance and notification to that effect is earnestly requested. The Examiner is invited to telephone Applicant's attorney (612-359-3261) to facilitate prosecution of this application.

If necessary, please charge any additional fees or credit overpayment to Deposit Account No. 19-0743.

Respectfully submitted,

PAVEL A. KRASUTSKY

By their Representatives,

SCHWEGMAN, LUNDBERG, WOESSNER & KLUTH, P.A.  
P.O. Box 2938  
Minneapolis, MN 55402  
(612) 359-3261

Date

8/1/02

By



Gary J. Speier

Reg. No. 45,458

CERTIFICATE UNDER 37 CFR 1.8: The undersigned hereby certifies that this correspondence is being deposited with the United States Postal Service with sufficient postage as first class mail, in an envelope addressed to: Commissioner of Patents, Washington, D.C. 20231, on this 2<sup>nd</sup> day of August, 2002.

Name

Dawn M. Poole

Signature

Dawn M. Poole

## **CLEAN VERSION OF ABSTRACT**

### **METHOD FOR MANUFACTURING BETULINIC ACID**

**Applicant: Pavel A. Krasutsky**

**Serial No.: 09/840,627**

#### **Abstract of the Disclosure**

The present invention provides a method for preparing an ester of betulin at the 3-position, e.g., betulin-3-acetate, including the selective alcoholysis of a betulin-3,28-diester, e.g., betulin-3,28-diacetate; a method for preparing betulin-3-acetate including (1) acetylating betulin to provide betulin-3,28-diacetate and (2) the alcoholysis of betulin-3,28-diacetate to provide betulin-3-acetate; and a method for preparing betulinic acid (1) acetylating betulin to provide betulin-3,28-diacetate, (2) the alcoholysis of betulin-3,28-diacetate to provide betulin-3-acetate, (3) oxidizing betulin-3-acetate to provide betulinic aldehyde-3-acetate, (4) oxidizing betulinic aldehyde-3-acetate to provide betulinic acid-3-acetate, and (5) deprotecting betulinic acid-3-acetate to provide betulinic acid.



**Clean Version of Pending Claims**

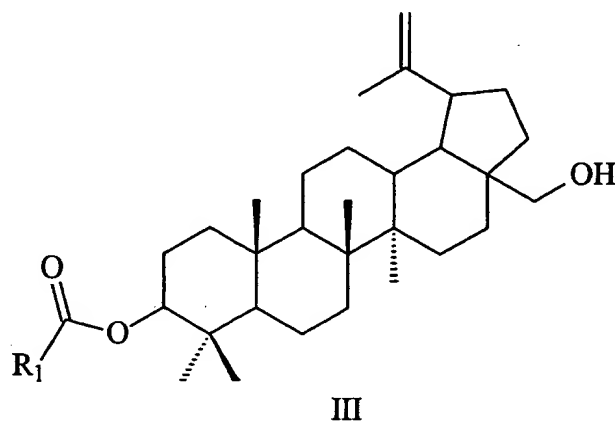
**METHOD FOR MANUFACTURING BETULINIC ACID**

Applicant: Pavel A. Krasutsky

Serial No.: 09/840,627

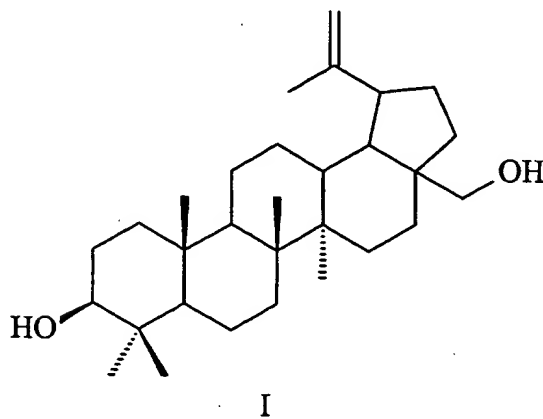
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1. (ONCE AMENDED) A process for preparing a compound of formula III

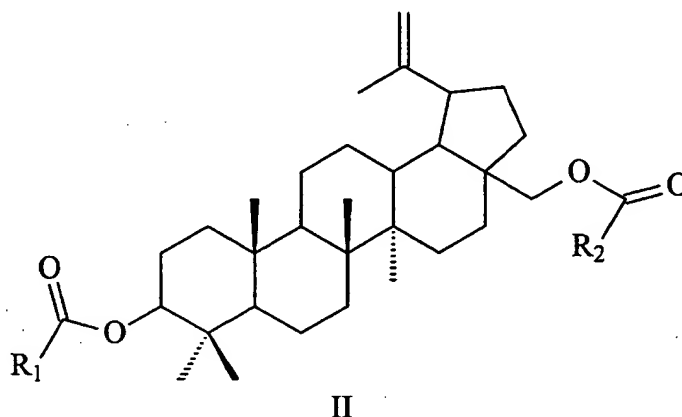


comprising:

- (1) acylating a compound of formula I



to provide a corresponding compound of formula II



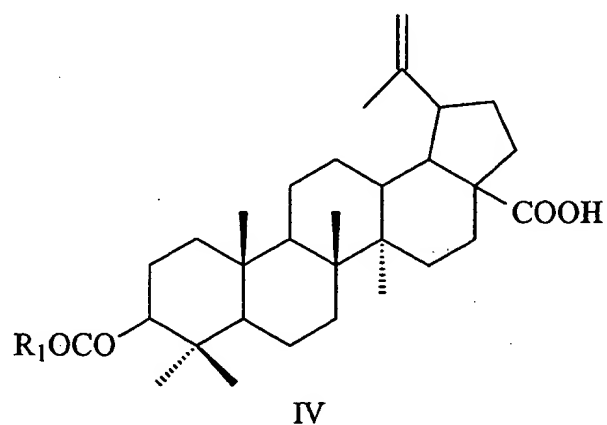
wherein  $R_1$  and  $R_2$  are each independently  $(C_1-C_{10})$ alkyl,  $(C_2-C_{10})$ alkenyl,  $(C_2-C_{10})$ alkynyl, or  $(C_6-C_{10})$ aryl, wherein any alkyl, alkenyl, alkynyl, or aryl of  $R_1$  and  $R_2$  can be optionally substituted with one or more halo, nitro, cyano, trifluoromethyl, hydroxy, SR or NRR, wherein each R is independently H or  $(C_1-C_{10})$ alkyl; and

(2) alcoholyzing a compound of formula II to provide a corresponding compound of formula III.

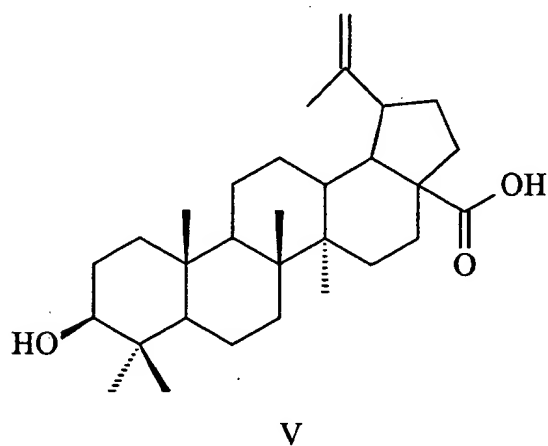
2. The process of claim 1 wherein the acylating comprises heating to reflux in acetic acid and acetic anhydride for about 2 hours to about 5 hours.
3. The process of claim 1 wherein the acylating comprises heating in pyridine and benzoyl chloride at about 50°C to about 60°C for about 20 hours to about 30 hours.
4. The process of claim 1 wherein the alcoholyzing comprises heating in the presence of an aluminum alkoxide and an anhydrous alcohol.

- 
- VI

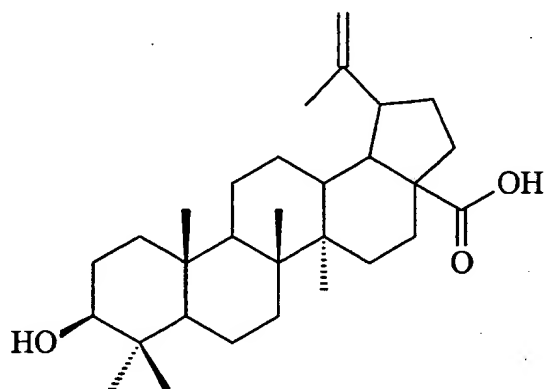
10. The process of claim 9 further comprising oxidizing the compound of formula VI to provide a compound of formula IV



11. The process of claim 10 further comprising deprotecting the compound of formula IV to provide a compound of formula V



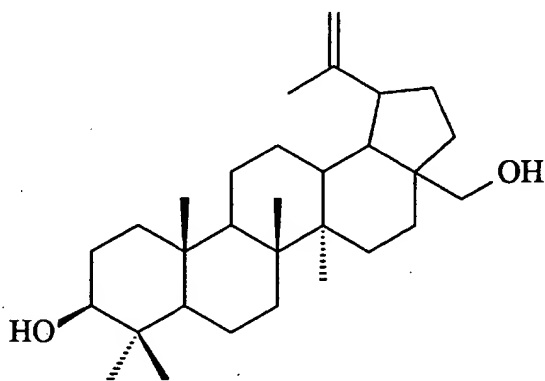
12. (ONCE AMENDED) A process for preparing the compound of formula V



V

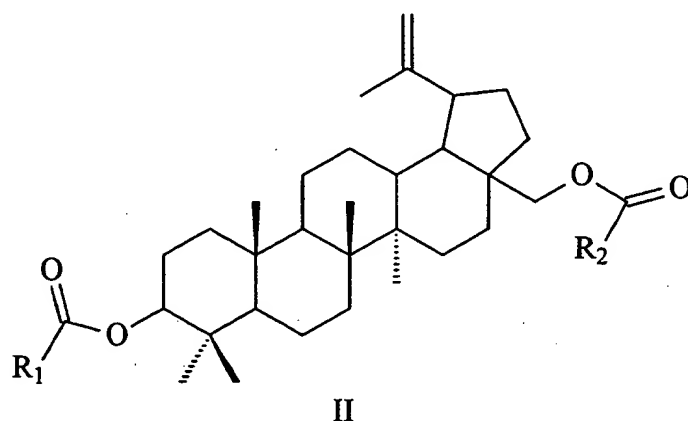
comprising:

(1) acylating a compound of formula I



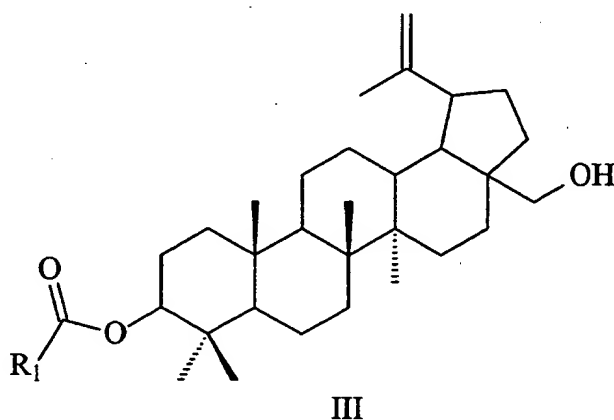
I

to provide a corresponding compound of formula II

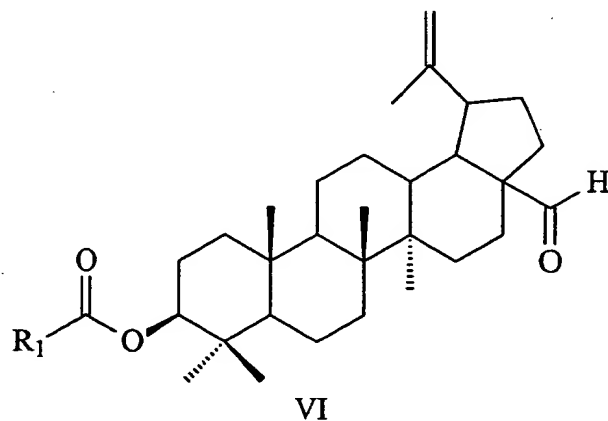


wherein  $\text{R}_1$  and  $\text{R}_2$  are each independently  $(\text{C}_1\text{-C}_{10})$ alkyl,  $(\text{C}_2\text{-C}_{10})$ alkenyl,  $(\text{C}_2\text{-C}_{10})$ alkynyl, or  $(\text{C}_6\text{-C}_{10})$ aryl, wherein any alkyl, alkenyl, alkynyl, or aryl of  $\text{R}_1$  and  $\text{R}_2$  can be optionally substituted with one or more halo, nitro, cyano, trifluoromethyl, hydroxy, SR or NRR, wherein each R is independently H or  $(\text{C}_1\text{-C}_{10})$ alkyl;

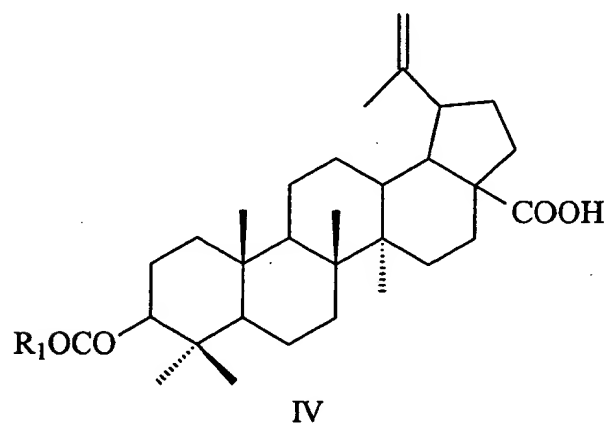
(2) alcoholizing a compound of formula II to provide a corresponding compound of formula III;



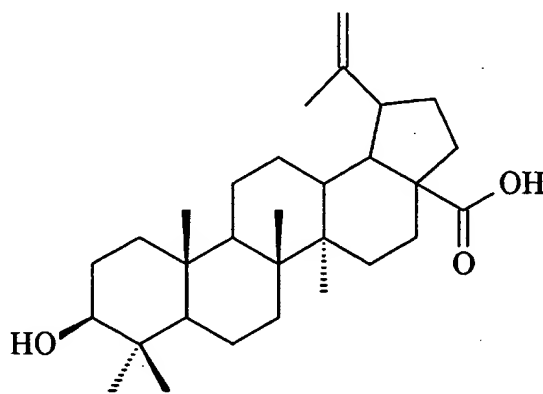
(3) oxidizing the compound of formula III to provide a corresponding compound of formula VI;



(4) oxidizing the compound of formula VI to provide a compound of formula IV;  
and



(5) deprotecting the compound of formula IV to provide the compound of formula  
V.



V

13. (ONCE AMENDED) The process of claim 12 wherein the alcoholizing is carried out for about 0.5 hours to about 5 hours.

14. The process of claim 12 wherein the alcoholizing comprises heating the compound of formula II in the presence of an aluminum alkoxide and an anhydrous alcohol.

15. The process of claim 14 wherein the aluminum alkoxide is aluminum isopropoxide.

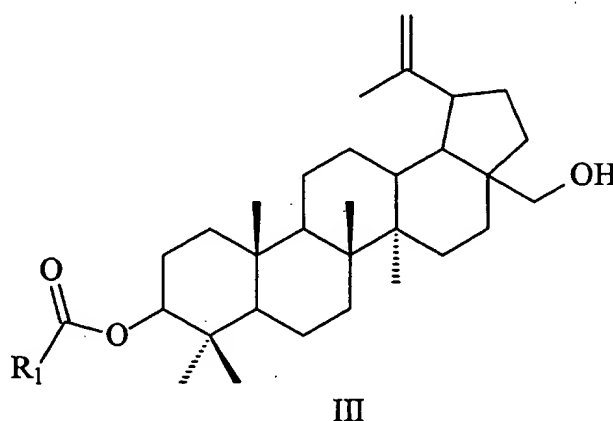
16. The process of claim 14 wherein the alcohol is isopropanol.

17. The process of claim 12 wherein the acylating comprises heating to reflux in acetic acid and acetic anhydride for about 2 hours to about 5 hours.

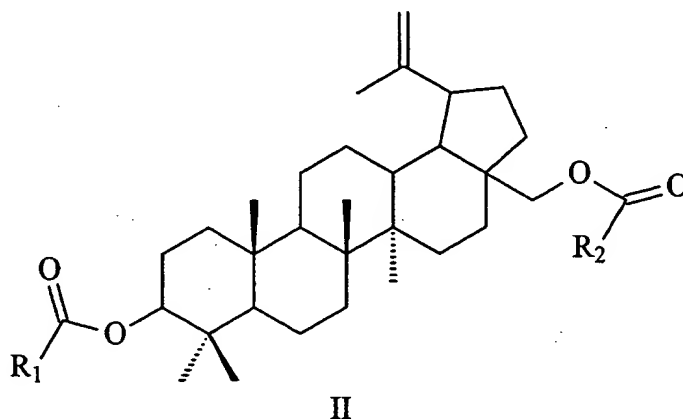
18. The process of claim 12 wherein the acylating comprises heating in pyridine and benzoyl chloride at about 50°C to about 60°C for about 20 hours to about 30 hours.



19. The process of claim 12 wherein the oxidizing of compound III to compound VI comprises palladium acetate, molecular sieves, and oxygen in trifluoromethylbenzene and pyridine at about 80°C to about 85°C for about 0.5 hour to about 4 hours.
20. The process of claim 12 wherein the oxidizing of compound VI to compound IV comprises oxygen and Cobalt (III) acetylacetonate in trifluoromethylbenzene at 60-65°C for about 0.5 hour to about 2 hours.
21. The process of claim 12 wherein the deprotecting comprises heating to reflux in methanol, water and sodium hydroxide.
22. (ONCE AMENDED) A process for preparing a compound of formula III



comprising: alcoholizing a corresponding compound of formula II



wherein  $R_1$  and  $R_2$  are each independently  $(C_1-C_{10})$ alkyl,  $(C_2-C_{10})$ alkenyl,  $(C_2-C_{10})$ alkynyl, or  $(C_6-C_{10})$ aryl, wherein any alkyl, alkenyl, alkynyl, or aryl of  $R_1$  and  $R_2$  can be optionally substituted with one or more halo, nitro, cyano, trifluoromethyl, hydroxy, SR or NRR, wherein each R is independently H or  $(C_1-C_{10})$ alkyl; to provide the compound of formula III.